APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>NDA</th>
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<td>211230</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>December 20, 2018</td>
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<tr>
<td><strong>OSE RCM #</strong></td>
<td>2018-1313</td>
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<tr>
<td><strong>Reviewer Name(s)</strong></td>
<td>Naomi Redd, Pharm.D.</td>
</tr>
<tr>
<td><strong>Team Leader</strong></td>
<td>Elizabeth Everhart, RN, MSN, ACNP</td>
</tr>
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<td><strong>Division Director</strong></td>
<td>Cynthia LaCivita, Pharm.D.</td>
</tr>
<tr>
<td><strong>Review Completion Date</strong></td>
<td>September 25, 2018</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of the Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>Solriamfetol</td>
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<tr>
<td><strong>Trade Name</strong></td>
<td>Sunosi</td>
</tr>
<tr>
<td><strong>Name of Applicant</strong></td>
<td>Jazz Pharmaceuticals</td>
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<tr>
<td><strong>Therapeutic class</strong></td>
<td>Dopamine and Norepinephrine Reuptake Inhibitor (DNRI)</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>75 mg, 150 mg oral tablets</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>Take one tablet once daily upon awakening</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Sunosi (solriamfetol) is necessary to ensure the benefits outweigh its risks. Jazz Pharmaceuticals submitted a New Drug Application (NDA) 211230 for solriamfetol with the proposed indication to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy and obstructive sleep apnea (OSA). The risks associated with solriamfetol include serious cardiovascular events, blood pressure and heart rate increases, psychiatric symptoms, and angle closure glaucoma. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK has determined that a REMS is not needed to ensure the benefits of solriamfetol outweigh its risks. The efficacy of solriamfetol was established in five randomized placebo-controlled studies (Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) clinical program). All trials showed superiority of solriamfetol relative to placebo. If approved, solriamfetol would provide another therapeutic option for the treatment of wakefulness in patients with narcolepsy and/or OSA. Adverse events such as cardiac events, blood pressure increases, and the potential for psychiatric events are not new or unusual events and are seen in other treatments for these disorders; thus, it would be expected that the prescribing population would be knowledgeable in the management thereof. The abuse potential for solriamfetol is like that of other Schedule IV drugs indicated in the management of wakefulness and narcolepsy.

This DRISK reviewer agrees with the Clinical Reviewer that a REMS is not needed to ensure the benefits outweigh the risk of solriamfetol.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME Sunosi (solriamfetol) is necessary to ensure the benefits outweigh its risks. Jazz Pharmaceuticals submitted a NDA 211230 for solriamfetol with the proposed indication to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy and OSA. The risks associated with solriamfetol include serious cardiovascular events, blood pressure and heart rate increases, psychiatric symptoms, and angle closure glaucoma. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Solriamfetol is a derivative of the amino acid phenylalanine and is a non-amphetamine wake-promoter. This derivative of the amino acid lacks the non-adrenergic releasing effects of amphetamines, and hence prevents hypersomnia.1 Dopamine and norepinephrine are wake-promoting neurotransmitters and have a role in sleep-wake regulation. Patients with narcolepsy and OSA have a dysfunction in this neurotransmitter system. Through the blockade of dopamine and norepinephrine transporters, solriamfetol enhances dopamine and norepinephrine signaling in the brainstem arousal systems. The mechanism(s) by which solriamfetol exerts its wake-promoting effects in humans are presumed to be
through its activity as a selective dopamine and norepinephrine reuptake inhibitor (DNRI). The proposed indication is to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy and OSA. The proposed dose is to initiate at

Solriamfetol is an NME\(^b\) and currently not approved in any other jurisdictions. Solriamfetol was granted orphan drug designation under the name “\(^b\)phenylalanine derivative” for narcolepsy.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 211230 relevant to this review:

- 12/20/2017: NDA 211230 submitted for solriamfetol
- 06/19/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for solriamfetol.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Narcolepsy is one of the most common causes of chronic sleepiness and affects approximately 1 in 2,000 people in the United States.\(^2\)\(^c\)\(^d\) This disorder usually begins between the ages of 10 and 20 years old, with the sudden or gradual onset of persistent daytime sleepiness. The diagnosis is often made only after serious problems have arisen such as poor performance at work or school, or a motor vehicle accident. Unlike those patients diagnosed with obstructive sleep apnea (OSA) who have poor-quality sleep, those with narcolepsy usually feel refreshed after a full night’s sleep or a brief nap, but their sleepiness returns 1 to 2 hours later, especially if they are sedentary.\(^2\)

Obstructive sleep apnea is a serious disorder characterized by sleep fragmentation caused by repeated wakefulness secondary to partial or complete obstruction of the upper airway during sleep. Risk factors for OSA generally include obesity, upper airway abnormalities, male gender, menopause and age (usually peaks at around age 55).\(^3\)

\(^a\) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

\(^b\) Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

\(^c\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

\(^d\) Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
3.2 **DESCRIPTION OF CURRENT TREATMENT OPTIONS**

Narcolepsy has no cure, but drug therapies and lifestyle changes are used to improve the quality of life to some extent. Medications used to improve wakefulness in patients with narcolepsy or OSA include: sodium oxybate (only has indication for narcolepsy), modafinil, and armodafinil (see the Appendix for more information on these medications). Stimulants such as methylphenidate and amphetamines have also been prescribed to improve wakefulness, however these medications come with a higher abuse potential than the later drugs approved, modafinil and armodafinil, in addition to severe adverse events. Lifestyle modifications such as regular napping, diet control and exercise are also used to help manage disease symptoms or treatment side effects.

In OSA, improving the functioning of the airways to stabilize the upper airway with air and prevent collapse of airways during sleep is the standard of care. These include Continuous Positive Airway Pressure (CPAP) machinery, an oral appliance, or a surgical intervention to treat their underlying obstruction. Modafinil and armodafinil are the only drugs approved to treat excessive sleepiness that can result from OSA.

4 **Benefit Assessment**

The efficacy of solriamfetol has been established in the Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) clinical program in five randomized placebo-controlled studies. All trials showed superiority of solriamfetol relative to placebo and included the following:

- Two 12-week trials in adults with excessive sleepiness due to narcolepsy (TONES 1 and TONES 2).
- One 12-week trial in adults with excessive sleepiness due to OSA (TONES 3).
- Two randomized-withdrawal trials, one assessing maintenance of effect after 4 weeks of treatment in adults with OSA (TONES 4) and one assessing maintenance of effect after at least 6 months of treatment in adults with narcolepsy or OSA (TONES 5).

**Narcolepsy**

The measures of efficacy were change from baseline to the last post-baseline assessment for TONES 1 and change from baseline to Week 12 for TONES 2 on: ability to stay awake as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT), patient-reported excessive sleepiness (ESS) as measured by the ESS (TONES 2 only), and patient-reported improvement in their overall clinical condition as assessed by the Patient Global Impression of Change (PGIC) scale (TONES 2 only). In TONES 1, patients with narcolepsy were randomized to receive 150 mg of solriamfetol once daily for Weeks 1 through 4 and 300 mg once daily for Weeks 5 through 12, or to receive placebo for the entire 12 weeks. Statistically significant improvements in the MWT (Table 3), from baseline to the last post-baseline assessment were seen in the solriamfetol group compared with the placebo group.

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*Section 505-1(a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*
In TONES 2 patients with narcolepsy were randomized to receive solriamfetol (75 mg, 150 mg, or 300 mg) or placebo once daily, using stratified randomization based on the presence or absence of cataplexy. Patients randomized to the 150 mg and 300 mg dose arms received 75 mg and 150 mg, respectively, for the first 3 days before escalating to the assigned dose.

At Week 12, patients randomized to the 150 mg and 300 mg dose arms showed statistically significant improvements on the MWT and ESS, as well as on the PGIc compared with placebo. Patients randomized to receive 75 mg failed to show statistically significant improvement. The magnitude of effect was dose-dependent and was maintained over the 12 weeks of treatment on both the MWT and ESS. At Week 12, 150 mg and 300 mg of solriamfetol demonstrated sustained improvements in wakefulness throughout the day that were statistically significant compared to placebo as assessed in trials 1 through 5 of the MWT, spanning an approximate 9 hours following dose administration.

**Obstructive Sleep Apnea**

TONES 3, a 12-week multi-center, randomized, double blind, placebo-controlled study, established the efficacy of solriamfetol in improving wakefulness and reducing excessive sleepiness in patients diagnosed with OSA according to ICSD-3 criteria.

The measures of efficacy in this study were change from baseline to Week 12 on: ability to stay awake as measured by mean sleep latency on the MWT, patient-reported excessive sleepiness as measured by the ESS, and patient-reported improvement in their overall clinical condition as assessed by the PGIc.

Patients were randomized to receive solriamfetol (37.5 mg, 75 mg, 150 mg, or 300 mg) or placebo once daily, using stratified randomization based on the patient’s adherence or non-adherence to a primary OSA therapy (adherent: 71%; non-adherent: 29%). Patients randomized to the 150 mg and 300 mg dose arms received 75 mg and 150 mg, respectively, for the first 3 days before escalating to the assigned dose. At Week 12, patients randomized to the 75 mg, 150 mg, and 300 mg dose arms showed improvements on the MWT, ESS, and PGIc that were statistically significant compared to placebo. The magnitude of effect was dose-dependent and was maintained over the 12 weeks of treatment on both the MWT and ESS.

At Week 12, patients who were randomized to receive 75 mg, 150 mg, and 300 mg of solriamfetol demonstrated sustained improvements in wakefulness throughout the day that were statistically significant compared to placebo as measured in trials 1 through 5 of the MWT, spanning an approximate 9 hours following dose administration. Adherence/non-adherence to primary OSA therapy did not suggest evidence of differential efficacy.

**Maintenance of Efficacy in narcolepsy and OSA**

The maintenance of effect of solriamfetol in patients with narcolepsy and OSA was established in two randomized-withdrawal, placebo-controlled studies (TONES 4 and TONES 5). The measures of efficacy were change from the beginning to the end of the randomized-withdrawal period on: the ability to stay awake as measured by mean sleep latency on the MWT (TONES 4 only), patient-reported excessive
sleepiness as measured by the ESS, and patient-reported worsening in their overall clinical condition as assessed by the PGIc.

TONES 4 was a 6-week, multi-center, randomized-withdrawal, double-blind, placebo-controlled, study of the efficacy of solriamfetol in adult patients with a diagnosis of OSA based on ICSD-3 criteria.

TONES 5 established the long-term safety and maintenance of effect for up to a year of treatment with solriamfetol, including a 2-week randomized-withdrawal period after at least 6 months of treatment with solriamfetol in patients with narcolepsy or OSA who had completed a prior trial.

During the randomized-withdrawal period, patients who continued to receive solriamfetol maintained their treatment benefit with little change on the ESS. In comparison, those randomized to placebo had a worsening on the ESS (higher score) and in their overall clinical condition (PGIc), resulting in a statistically significant difference in maintenance of efficacy between solriamfetol and placebo.

For patients who were using a primary OSA therapy at the beginning of the TONES 5 study, primary OSA therapy use (percentage of nights used per week) did not change over the course of the 40- or 52-week study.

The clinical reviewer is recommending approval for the treatment of excessive daytime sleepiness in narcolepsy is 150 mg and 300 mg doses, and approval of the 75 mg, 150 mg, and 300 mg doses for treatment of excessive daytime sleepiness in OSA.

5 Risk Assessment & Safe-Use Conditions\textsuperscript{1,\textit{f},\textit{g},\textit{h}}

At the time of this review, safety and labeling negotiations were still ongoing.

Solriamfetol has been evaluated for safety in 930 patients (ages 18-75 years) with excessive sleepiness associated with narcolepsy or OSA. Among these, a total of 573 patients were treated with solriamfetol in 12-week placebo-controlled trials in patients with excessive sleepiness associated with narcolepsy or OSA at doses of 37.5 mg (OSA only), 75 mg, 150 mg, and 300 mg once daily. The most common adverse reactions (incidence ≥5%) reported more frequently with the use of solriamfetol than placebo were headache, nausea, decreased appetite, anxiety, diarrhea, dry mouth, and insomnia. Many of these

\textsuperscript{f} Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

\textsuperscript{g} Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

\textsuperscript{h} Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
events were mild to moderate in severity and occurred within the first 2 weeks of initiating solriamfetol, and resolved on their own.

Serious adverse events of solriamfetol include: blood pressure and heart rate increases, and the potential for psychiatric events. These adverse events will be communicated in the Warnings and Precautions section of the product label. At this time there is no Boxed Warning proposed for solriamfetol.

### 5.2 BLOOD PRESSURE AND HEART RATE INCREASES

In the clinical trials for solriamfetol, there were changes in blood pressure and heart rate that were dose dependent. In the patients who were on antihypertensive medications in these trials, 2.4% had an increase in their antihypertensive medication dose, an addition of a new antihypertensive medication, or were switched to a different antihypertensive medication to control blood pressure. In the placebo arm, 1.3% of patients had the aforementioned changes in their anti-hypertensive meds as discussed above. Recommendations in the label are measure heart rate and blood pressure prior to initiating treatment with solriamfetol, and that pre-existing hypertension should be controlled before initiating therapy with solriamfetol. The label will also recommend to discontinue solriamfetol if patients experience sustained increases in blood pressure or heart rate that cannot be managed with appropriate medical intervention or dose reduction of solriamfetol.

### 5.3 PSYCHIATRIC EVENTS

Anxiety, insomnia, irritability and agitation have been observed in the clinical trials for solriamfetol. Solriamfetol has not been evaluated in patients with psychosis or bipolar disorders. The label recommends using caution when treating patients with solriamfetol who have a history of psychosis or bipolar disorders, and patients should be observed for the possibility of emerging psychiatric symptoms or an exacerbation of a pre-existing psychiatric condition. Recommendations in the label are to manage these events are either to reduce the solriamfetol dose or discontinue solriamfetol should these events occur.
5.4 DRUG ABUSE AND DEPENDENCE
The abuse potential of solriamfetol in doses of 252 mg, 504 mg and 1008 mg was assessed relative to phentermine (45mg and 90mg) in a human abuse potential study in patients experienced with drugs of abuse. Results from this clinical study demonstrated that solriamfetol produced psychoactive and euphoric effects and feelings consistent with or less than phentermine, which is a Schedule IV controlled substance. Recommendations in the label are that Physicians should carefully evaluate patients for a recent history of drug or alcohol abuse and follow such patients closely, observing them for signs of misuse or abuse of solriamfetol.

6 Expected Postmarket Use
Due to the nature of narcolepsy and OSA, solriamfetol has the potential to be prescribed by a wide variety of health practitioners, including family practice physicians, internists, and mid-level providers such as nurse Practitioners and Physicians Assistants to patients in an ambulatory care setting.

7 Risk Management Activities Proposed by the Applicant
The Applicant did not propose any risk management activities for solriamfetol beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS
Excessive sleepiness because of narcolepsy and OSA can be a disabling symptom that is associated with clinical conditions that may decrease an individual’s quality of life. Certain medications in addition to lifestyle changes can improve symptoms and quality of life in some patients. The medications currently approved to increase wakefulness in patients with narcolepsy and/or OSA vary in their mechanism of actions and side effect profiles. Traditionally, stimulants such as amphetamines and methylphenidate were used due to their wake promoting effects, however, side effects such as cardiovascular events and their high potential for abuse (Schedule II controlled substances) make these medications less desirable as first line treatment options. Newer wake-promoting drugs such as modafinil and armodafinil have a lower abuse potential (Schedule IV), however there are still adverse events that must be considered when initiating treatment. Sodium oxybate is another drug in the treatment armamentarium, however, this drug comes with a higher abuse potential in addition to severe adverse events such as CNS and respiratory depression and other psychiatric events. Sodium oxybate has a Boxed Warning, and is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risk of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of sodium oxybate. None of the other drugs approved for the treatment of wakefulness in patients with narcolepsy or OSA have a Boxed Warning or was approved with a REMS.

If approved, solriamfetol would provide another therapeutic option for the treatment of wakefulness in patients with narcolepsy and/or OSA. Adverse events such as cardiac events, blood pressure increases, and the potential for psychiatric events are not new or unusual events that have not been seen in other
treatments for these disorders, thus, it would be expected that the prescribing population would be knowledgeable in the management thereof. The abuse potential for solriamfetol is like that of other Schedule IV drugs used in the management of wakefulness and narcolepsy. The efficacy of solriamfetol was established in five randomized placebo-controlled studies (Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) clinical program). All trials showed superiority of solriamfetol relative to placebo.

The Clinical Reviewer recommends approval of solriamfetol for excessive daytime sleepiness due to narcolepsy based on efficacy at the 150 mg and 300 mg doses, and at the 75 mg, 150 mg and 300 mg dose for excessive daytime sleepiness due to OSA, there are no safety findings identified that would preclude approval of this NDA, and that labeling is sufficient to communicate the risk, and therefore a REMS is not needed.

This DRISK reviewer agrees with the Clinical Reviewer that a REMS is not necessary to ensure the benefits outweigh the risks for solriamfetol. Labeling will be used to communicate the risks for solriamfetol.

9 Conclusion & Recommendations

Based on the clinical review available data and clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for solriamfetol to ensure the benefits outweigh the risks. The safety concerns associated with solriamfetol have been documented with the use of other therapies for the treatment of wakefulness in patients with narcolepsy or OSA. Healthcare providers who treat these conditions are likely to be familiar with the risks of these drugs and the importance of patient monitoring. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated if necessary.
## 10 Appendices

### 10.1 Safety Profile of Drugs for the Treatment of Excessive Sleepiness in Narcolepsy and OSA

<table>
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<tr>
<th></th>
<th>Solriamfetol&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Sodium Oxybate&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Modafinil&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Armodafinil&lt;sup&gt;4&lt;/sup&gt;</th>
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<td><strong>Indication</strong></td>
<td>To improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy and OSA</td>
<td>Treatment of cataplexy and excessive sleepiness&lt;sup&gt;(b)(d)&lt;/sup&gt; with narcolepsy</td>
<td>To improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder</td>
<td>To improve wakefulness in adult patients with excessive sleepiness associated with OSA, narcolepsy, or shift work disorder</td>
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<td><strong>Schedule</strong></td>
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<td><strong>Dose</strong></td>
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<td>4.5g – 9g orally at bedtime taken in 2 equal divided doses, 4 hours apart</td>
<td>100-200mg orally once a day in the morning</td>
<td>150mg – 250mg orally once daily</td>
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<td><strong>REMS?</strong></td>
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<td>Yes; ETASU</td>
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<td><strong>Boxed Warning?</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td><strong>Warnings and Precautions</strong></td>
<td>(&lt;sup&gt;b&lt;/sup&gt;(d)</td>
<td>5.1 – CNS depression; use in caution with other CNS depressants &amp; with caution in patients operating hazardous machinery or activities requiring mental alertness</td>
<td>5.1 – Rash/Stevens-Johnson Syndrome</td>
<td>5.1 – Serious Dermatologic Reactions</td>
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<td>5.2 – Abuse &amp; Misuse</td>
<td>5.2 – Angioedema/ anaphylaxis</td>
<td>5.2 – Multiorgan hypersensitivity</td>
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<td>5.3 – Multi-organ hypersensitivity</td>
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<td>5.4 – Respiratory depression/sleep-disordered breathing</td>
<td>5.5 – Psychiatric symptoms</td>
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<td>5.5 – Depression/Suicide</td>
<td>5.6 – Effects on ability to drive and use machinery</td>
<td>5.6 – Effects on ability to drive and use machinery</td>
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<td>5.6 – Behavioral/Psychiatric events</td>
<td>5.7 – Cardiovascular events</td>
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<td>5.7 – Parasomnias</td>
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<td></td>
<td></td>
<td>5.8 – Excessive sodium intake</td>
<td></td>
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</tbody>
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10.2 REFERENCES

1 Solriamfetol FDA Draft Prescribing Information, August 8, 2018


3 Lurie A. Obstructive Sleep Apnea in Adults. Adv Cardiol. 2011, vol 46, pp 1-42

4 Xyrem (sodium oxybate) US Prescribing Information, Jazz Pharmaceuticals, Inc., January 2017

5 Provigil (modafinil) US Prescribing Information, Teva Pharmaceuticals USA, Inc., February 2015

6 Nuvigil (armodafinil) US Prescribing Information, Teva Pharmaceuticals USA, Inc., February 2017
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAOMI B REDD
09/28/2018

ELIZABETH E EVERHART
09/28/2018
I concur

CYNTHIA L LACIVITA
09/28/2018